Optimizing the differentiation and expansion of microglial progenitors from human pluripotent stem cells for the study and treatment of neurological disease.

Grant Award Details

Optimizing the differentiation and expansion of microglial progenitors from human pluripotent stem cells for the study and treatment of neurological disease.

Grant Type: Tools and Technologies III

Grant Number: RT3-07893

Project Objective: To generate and use pluripotent fluorescent reporter lines to streamline this process and develop fully-defined microglial differentiation protocols. It is also critical to determine whether human induced pluripotent stem cell-derived microglia can be used to study or potentially treat human neurological disease. As a proof-of-principle, the team will therefore examine the role of the Alzheimer's disease-associated gene CD33 in human microglial function and use novel xenotransplantation-compatible AD mice to examine the functional effects of human microglia transplantation in vivo.

Investigator:

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Type:	PI

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Name:	Colin Pouton
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Type:	Partner-PI

Disease Focus: Alzheimer's Disease, Neurological Disorders

Collaborative Funder: Australia

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $1,147,596

Status: Active

Progress Reports

Reporting Period: Year 1

View Report

Grant Application Details

Application Title: Optimizing the differentiation and expansion of microglial progenitors from human pluripotent stem cells for the study and treatment of neurological disease.

Public Abstract: Microglia are a type of immune cell within the brain that profoundly influence the development and progression of many neurological disorders. Microglia also inherently migrate toward areas of brain injury, making them excellent candidates for use in cell transplantation therapies. Despite the widely accepted importance of microglia in neurological disease, methods to produce microglia from stem cells have yet to be reported. Our team has recently developed one of the first protocols to generate microglia from human pluripotent stem cells. We have used several approaches to confirm that the resulting cells are microglia including examination of gene expression and testing of key microglial functions. However, our current protocol uses cell culture supplements that preclude the use of these cells for any future clinical applications in people. The major goal of this proposal is to resolve this problem. We will generate pluripotent human stem cells that have special "reporter" genes that make the cells glow as they become microglia, allowing us to readily monitor and quantify the generation of these important cells. Using these reporter lines we can then streamline the differentiation process and develop improved protocols that could be translated toward eventual clinical use. As a proof-of-principle experiment we will then use the resulting human microglia to study some important questions about the genetic causes and potential treatment of Alzheimer's disease.

Statement of Benefit to California: Recent estimates suggest that nearly 2 million Californian adults are currently living with a neurological disorder. While the causes of neurological disease vary widely from Alzheimer's disease to Stroke to Traumatic Brain Injury, a type of brain cell called microglia has been strongly implicated in all of these disorders. Microglia are often considered the immune cell of the brain, but they play many additional roles in the development and function of the nervous system. In neurological disease, Microglia appear to be involved in a response to injury but they can also secrete factors that exacerbate neurological impairment. Unfortunately, it has been difficult to study human microglia and their role in these diseases because of challenges in producing these cells. Our group recently developed an approach to 'differentiate' microglia from human pluripotent stem cells. This enables researchers to now study the role of different genes in human microglial function and disease. Yet our current approach dose not allow these cells to be used for potential clinical testing in patients. Our proposal therefore aims to develop new tools and technology that will allow us to produce clinically-relevant human microglia. These cells will then be used to study the role of a specific microglial gene in Alzheimer's disease, and may ultimately be useful for developing treatments for the many Californians suffering from neurological disease.